Designing gradient plotted scaffolds as a tool for improving osteochondral regeneration

10. Valorization

The research conducted into the laboratories of research centers and universities might often be disconnected from the business world. This generates often, difficulties in valorizing the work conducted in these laboratories and put the scientists in a challenging position to develop their idea into a working marketable concept [1]. The process of identifying a valuable idea and translate it into a product, which has an impact on the market and the society, is called “technology transfer” or “knowledge valorization”. Universities, companies and government organizations are supported by technology transfer offices. Their role is to identify which research has potential commercial interest and how to best develop and use it [2].

In the present thesis, the effect of scaffolds with in-built gradient on human mesenchymal stem cells (hMSCs) differentiation was analyzed in order to mimic the gradual transition from the subchondral bone toward the cartilage tissue found at the joint surface.

Some scaffolds designs showed more promising results, which may be easier to valorize. In chapter 6 the use of scaffolds presenting axial pore architecture gradients showed a potential in the effect of promoting the differentiation of hMSCs. In the following section I will propose some ways in which the findings of this chapter could be valorized. In particular, I will focus on the social and clinical relevance of our research. Subsequently, I will focus on the novelty of the scaffold design and its possible applications.

Social and clinical relevance

The osteochondral tissue is located at the end of the long bones and allows the transition from the hard mineralized bone to the soft and highly hydrated cartilage. It is possible to identify different zones within this transition tissue. Shortly, from the bottom to the top of the osteochondral tissue we first encounter the subchondral bone, followed by calcified cartilage. From this point, the cartilage starts dividing into the deep zone, the middle zone and the articular surface. This stratification

translates in a gradient variation of characteristics such as stiffness, cellularity and biochemical composition.

Osteoarthritis (OA), the degeneration of the osteochondral tissue, is estimated to be worldwide the fourth leading cause of disability and the most common self-reported cause of disability in activities of daily living [3, 4]. According to the Centers for Disease Control and Prevention (CDC), about 27 million people in the United States have osteoarthritis. The disease is a progressive degeneration of the joint which starts with subtle biochemical changes, leading to a gross cartilage loss and morphological damage of other joint tissues [5]. During the onset of osteoarthritis the collagen matrix becomes more disorganized and the proteoglycan content in cartilage decreases. These changes generate a major increase in water content. Since the protection effect of proteoglycan is lost, collagen fibers begin to undergo degradation generating a domino effect, which can lead to inflammation and pain [6-8]. Current treatments rely on surgery and present several drawbacks, and sometimes as in case of osteotomy are helping in pain relief and retardation of OA onset, but are not effective in the long term [9].

Novelty

Rapid prototyping has emerged in the last decades in the field of tissue engineering and regenerative medicine for its versatility and possible applications. The scaffolds are generated in a layer by layer manner ensuring a fully interconnected pore structures with tunable pore size and shape. Additionally, structural parameters like the diameter, distance and orientation of the struts can be tuned during the production process [10]. Typically, the fiber deposition pattern is used to vary the direction of the fibers every layer, leading to pores with honeycomb shaped obtained after several layers [11]. In chapter 6 the pattern 0-*a*-0-*a* was used (for example 0-45-0-45) in order to have a pore defined by 2 subsequent layers and have a constant pore shape for 6 layers. The novelty of this simple design is the generation of a reproducible repetitive unit which, within a scaffold zone, is constant in all the directions. With such a constant structure all the cell residing in a scaffold portion experience the same geometrical cues, allowing

an easy interpretation of the relationship between pore geometry and hMSC differentiation.

The link between the novel design and its possible application results from the behavior of hMSCs residing in the different scaffold sections. Under chondrogenic conditions squared pores (0-90) enhanced the differentiation toward a chondrogenic lineage, whereas moving toward the portion of the scaffold with the elongated rhomboidal shape this expression decreased. Conversely under osteogenic conditions, osteogenic markers expression was prominent in the long rhomboidal pores (0-15) and decreased moving toward the square pore region. Usually the differentiation tests are conducted under osteogenic or chondrogenic conditions *in vitro*. hMSCs in our scaffolds followed the just described differentiation pattern also when cultured in a media containing both the osteogenic and chondrogenic stimuli.

Possible application

One of the most promising and effective biological based therapies for OA is autologous chondrocyte implantation, where the chondrocytes of the patient are harvested from a biopsy of health cartilage, expanded *ex vivo* and re-implanted in the defect following debridement. Despite reported good outcomes, this technique is highly time consuming due to the chondrocyte expansion from the cartilage biopsy. Additionally the patients have to go through several operations.

With our pore shape gradient scaffold, the number of intervention and time can be considerably reduced. We propose the removal of the damaged cartilage and subchondral bone portion with a biopsy. From the CT scan of the area to be removed we acquire the code to print a scaffold with the same shape of the removed portion with the pore shape gradient along the z axis. The scaffold can be produced under aseptic conditions or sterilized immediately after manufacturing. The scaffold will be placed in the hole generated by the biopsy with the 0-15 pores in contact with the subchondral bone and the squared pores at the cartilage surface. After implantation, the scaffold will be filled with the bone marrow that can be accessed through microfracturing of the underlying subchondral bone. This will

be the source of the hMSCs, which over time will populate the scaffold. The osteogenic and chondrogenic signals necessary to the hMSCs to differentiate will be provided by the surrounding tissues. This one step operation will reduce the time and discomfort caused by the harvesting of chondrocytes and their expansion before the actual reparative operation can be performed. Before translating this technique to the hospital and the market, additional studies in small and big animal models must be performed. Afterwards, additional clinical studies on sensitive patients should also be done to compare our scaffold with current therapies.

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